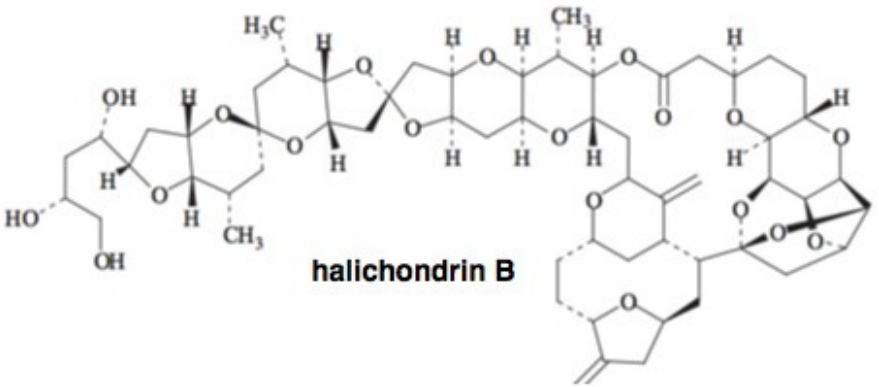
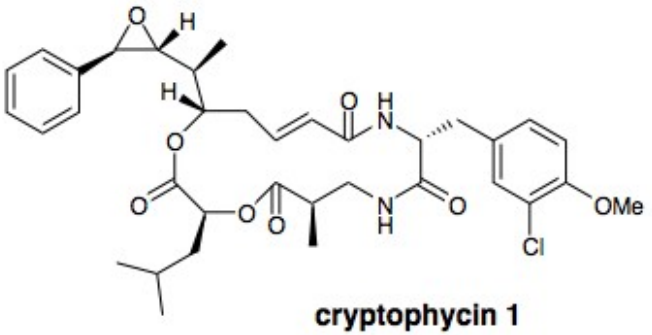

From the ocean...

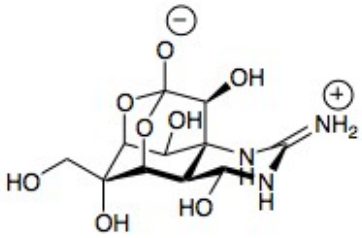
...to the clinic



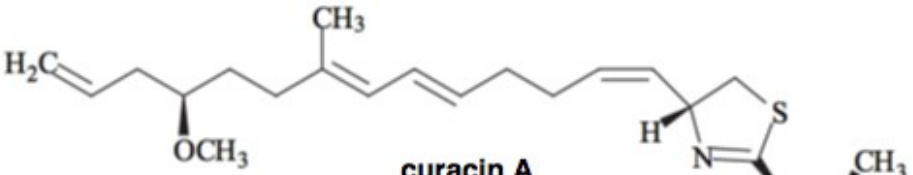
halichondrin B



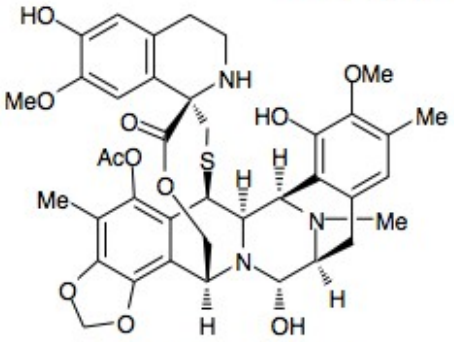
cryptophycin 1



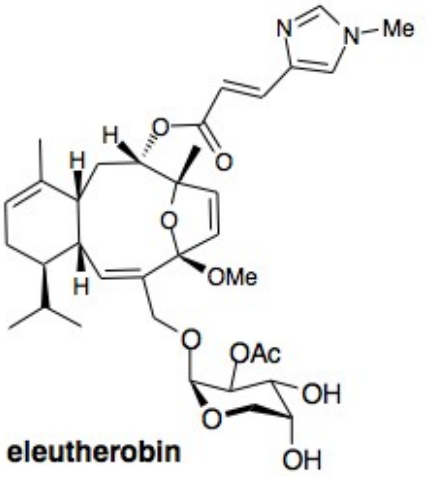
tetrodotoxin



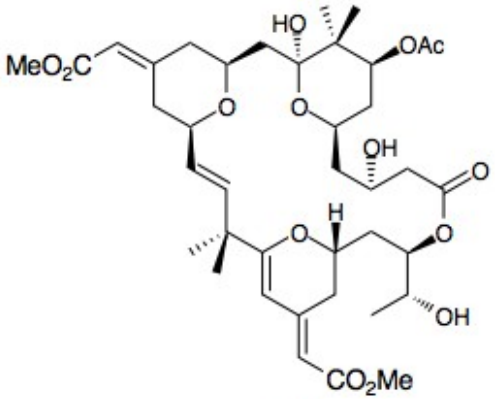
curacin A



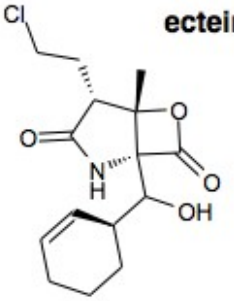
ecteinascidin 743



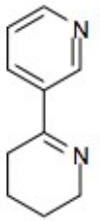
eleutherobin



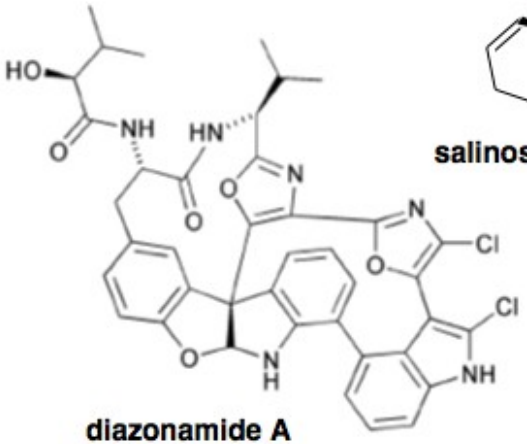
bryostatin 16



salinosporamide A



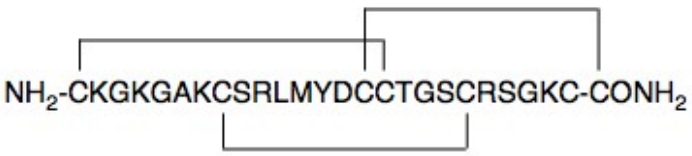
anabaseine



diazonamide A

Syntheses to be covered:

- Ecteinascidin 743 (Corey)
- Eleutherobin (Nicolaou)
- Salinosporamide A (Corey)
- Bryostatin 16 (Trost)



Ziconotide (Prialt®)

Lynbyga majuscula
Photograph courtesy of Ursula Keuper-Bennett and Peter Bennett
http://www.turtletrax.org

Halichondria okadai
Photograph: Yasunori Saito
University of Tsukuba, Shimoda Marine Research Center

Diazona violacea. The tropical congener *D. angulata* is a source of the compound Diazonamide A.
Photograph courtesy of Bernard Picton
Picton, B.E. & Morrow, 2005. Encyclopedia of Marine Life of Britain and Ireland
http://www.habitas.org.uk/marinelife

Eleutherobia sp.
Photograph courtesy of NSF
Photographer: M.H. Schleyer

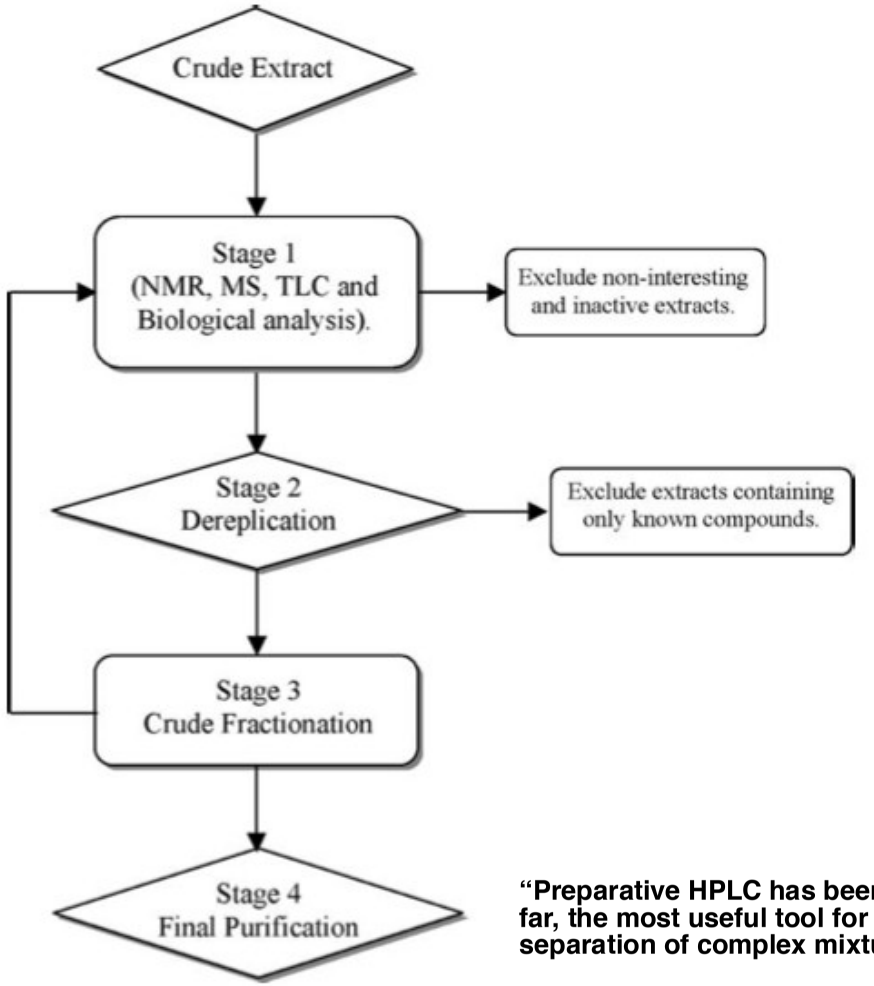
Ecteinascidia turbinata
Photograph courtesy of PharmaMar
http://www.pharmamar.com

paranemertes peregrina
Photograph courtesy of Mary Jo Adams
WSU/Beach Watchers
www.beachwatchers.wsu.edu

Dysidea arenaria. Note the unidentified cryptic nudibranch at the center of the image.
Photograph courtesy of Scott Johnson.

Photo by George Brooks
© Copyright 2002 California Academy of Sciences
Bugula neritina

Isolation of marine natural products



"Preparative HPLC has been, by far, the most useful tool for separation of complex mixtures."

Fig. 5. General approach for fractionation of marine extracts.

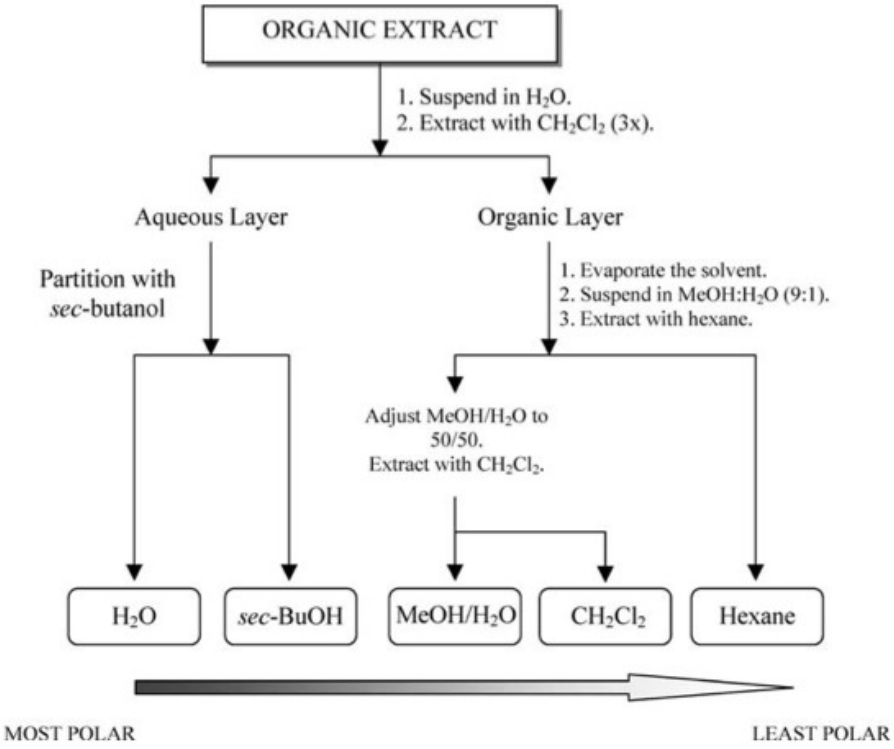


Fig. 6. Modified Kupchan's partition scheme.

Isolation of Marine Natural Products Wael E. Houssen and Marcel Jaspars. From: Methods in Biotechnology, Vol. 20, Natural Products Isolation, 2nd ed.

Isolation is hard: case studies

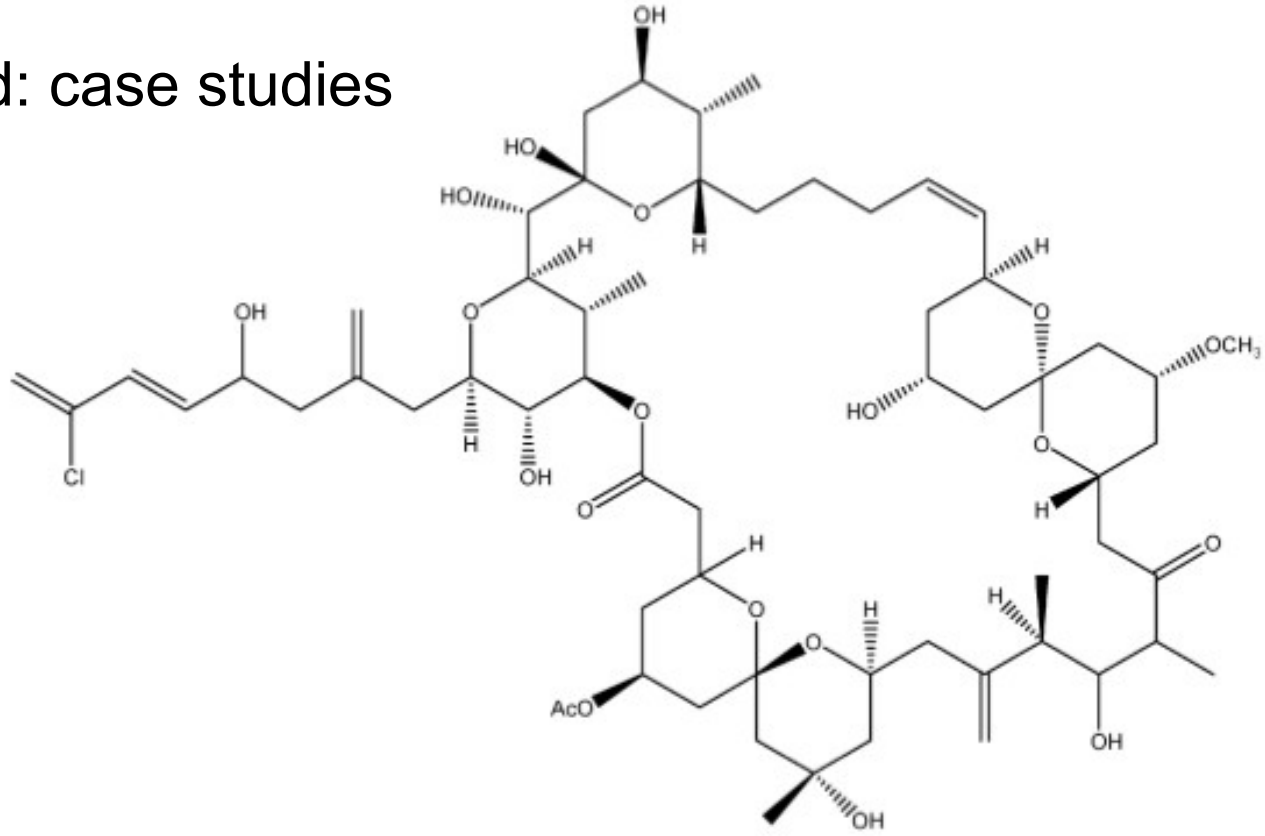


Fig. 1. Structure of spongistatin 4.

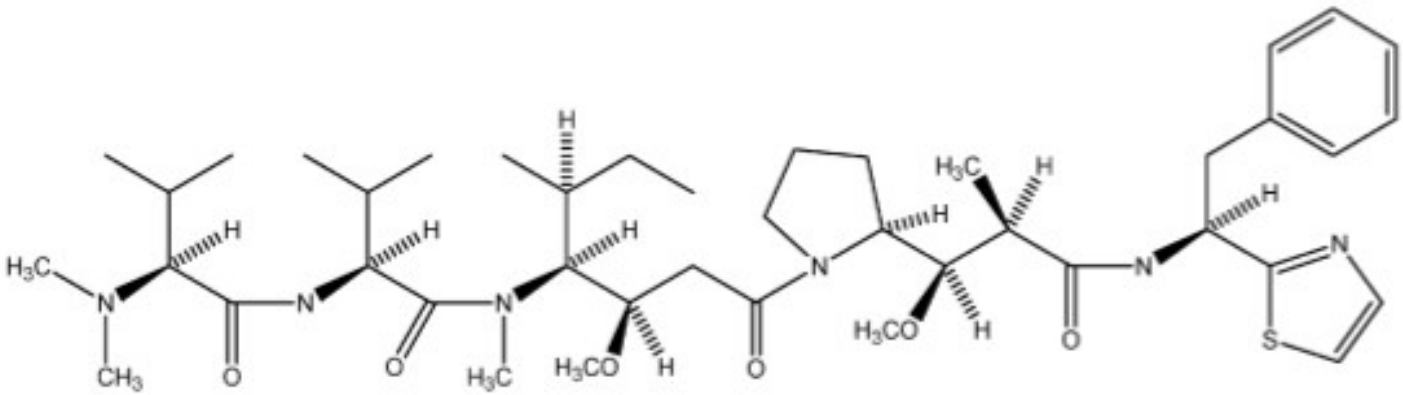
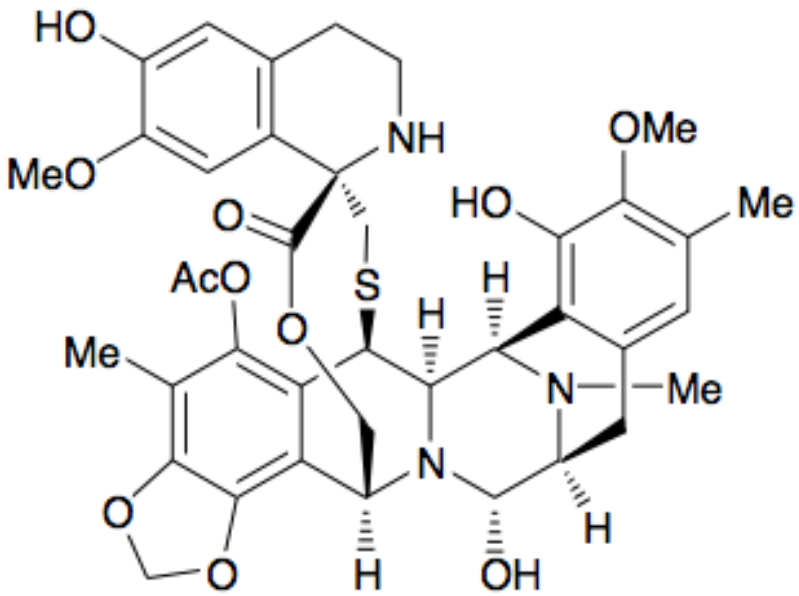


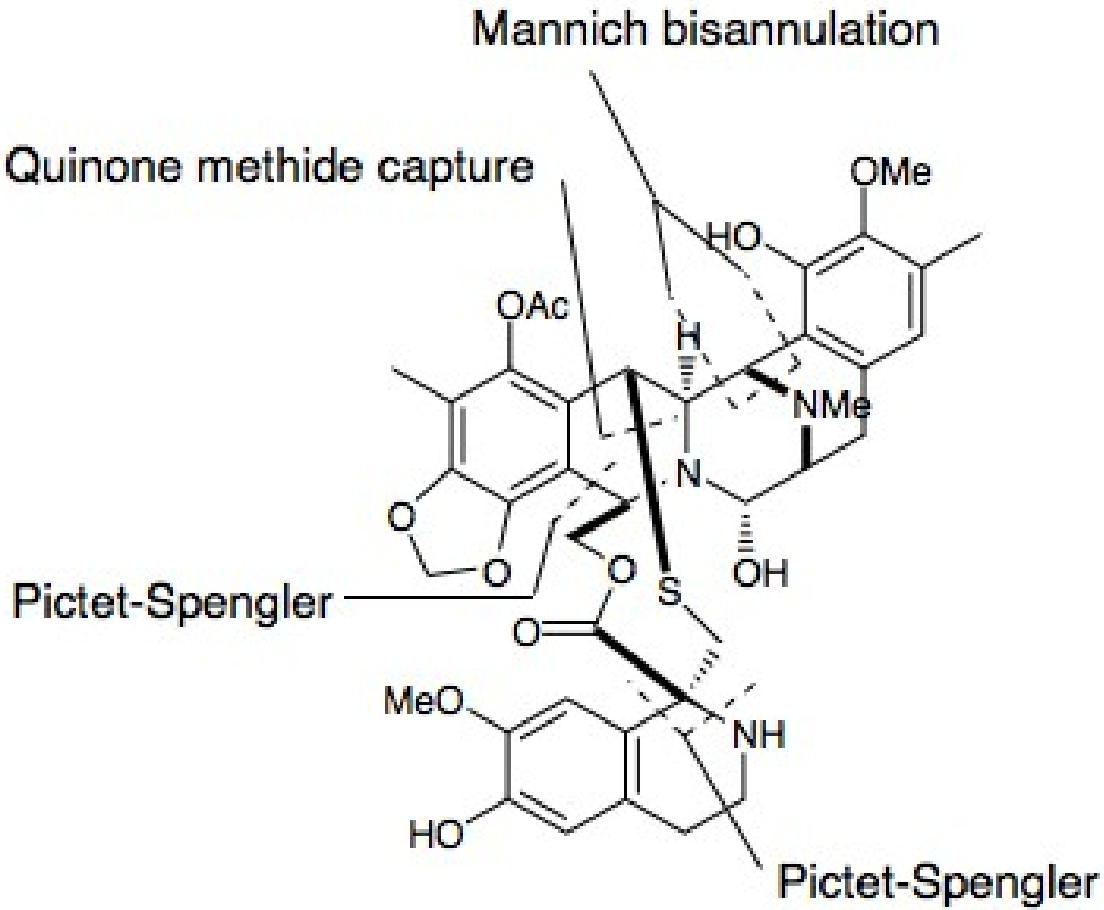
Fig. 2. Structure of dolastatin 10.



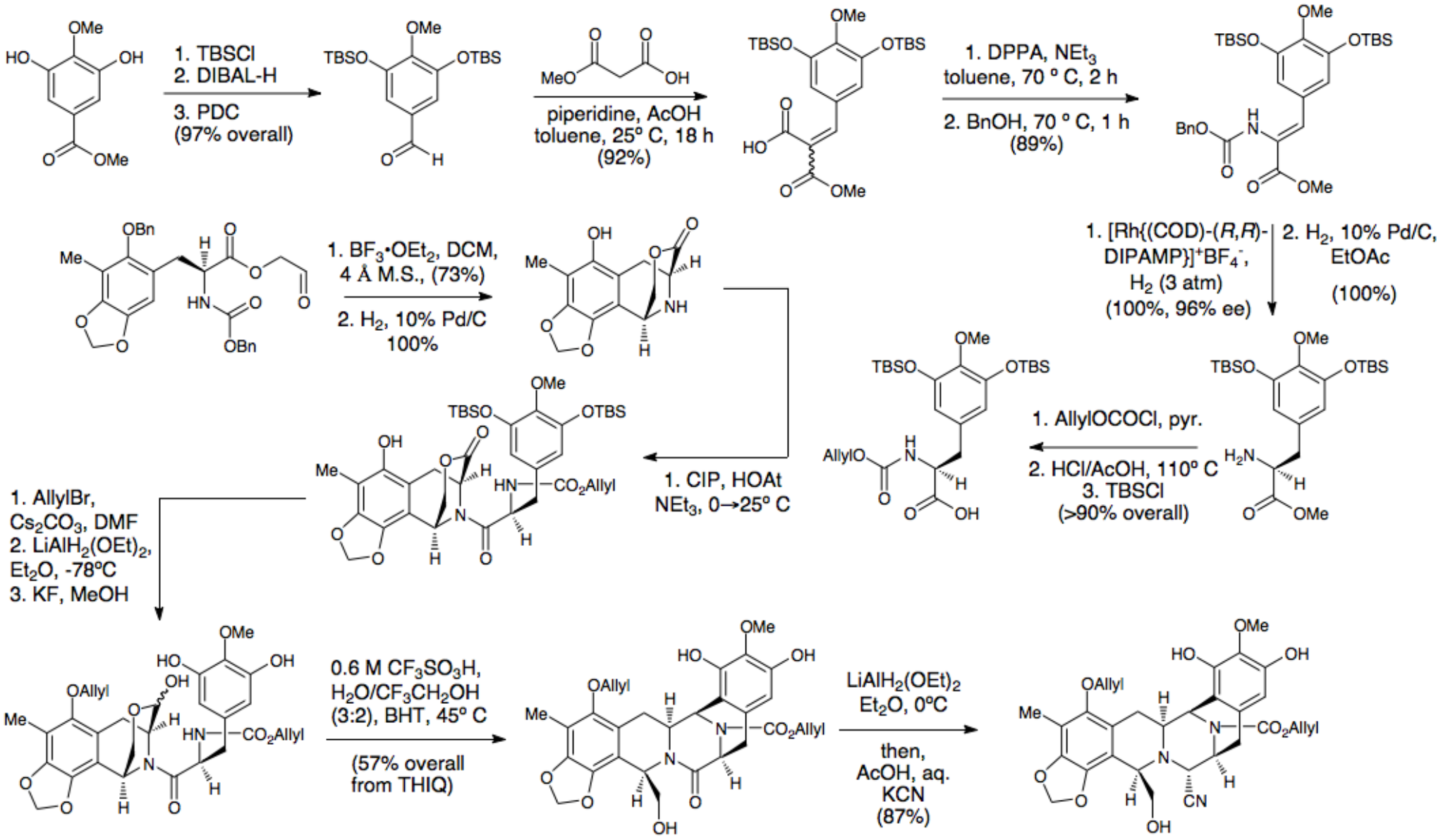
ecteinascidin 743

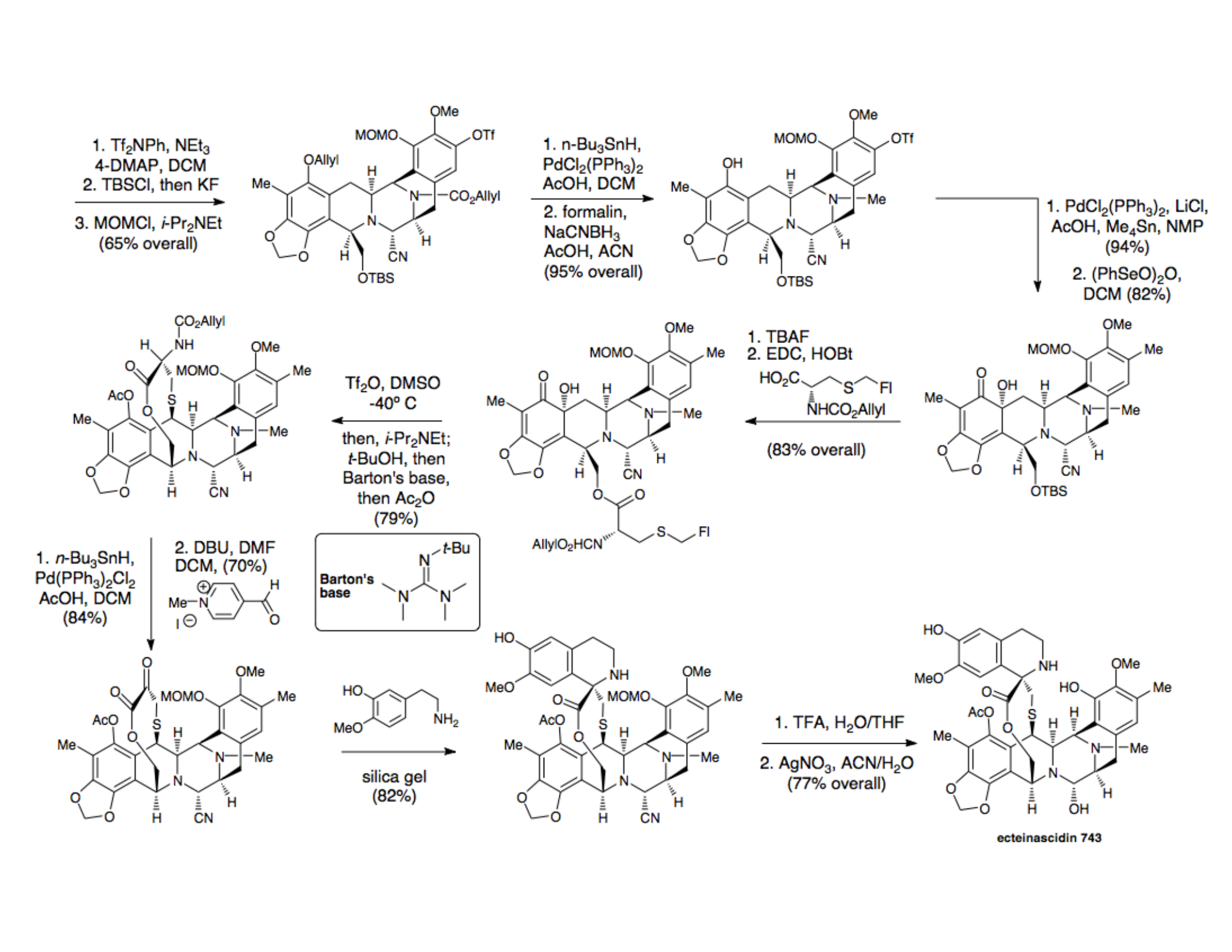
Ecteinascidia turbinata
Photograph courtesy of PharmaMar
http://www.pharmamar.com

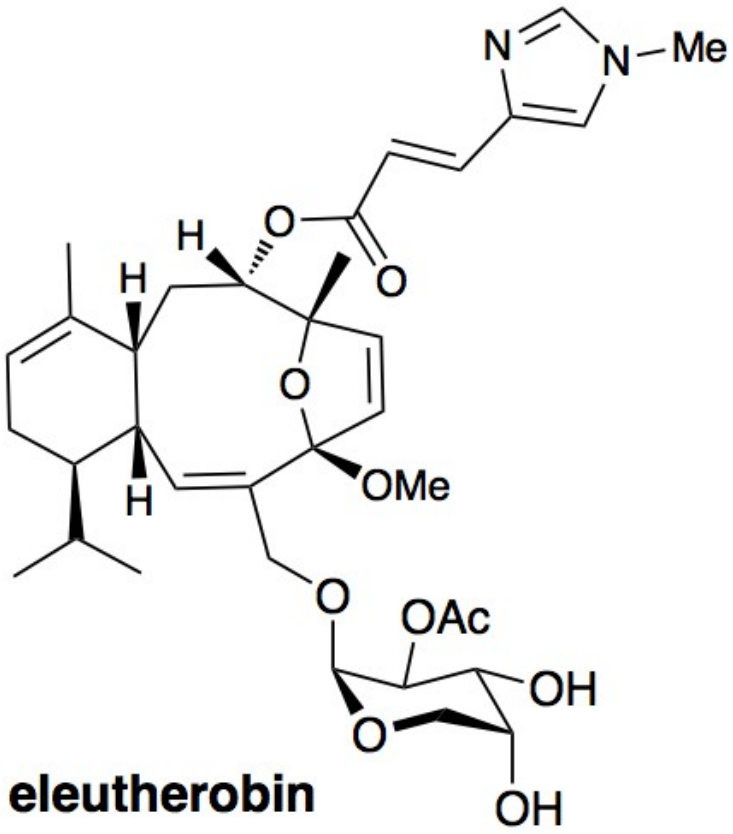
Isolation: First isolated from crude ethanolic extracts from *Ecteinascidia turbinata* in 1969. Extracts had potent cytotoxicity (picomolar to nanomolar range), but were not fully characterized until 1990.
Biosynthesis: Structurally related to saframycins. Postulated to come from two dimerized tryrosine residues, a cysteine residue, and subsequent Mannich and Pictet-Spengler condensations.
Total Synthesis: E.J. Corey, David Y. Gin, Robert S. Kania. *JACS.* **1996,** *118,* 9202-9203.
Mechanism of action: Binds in the minor groove of DNA and alkylates guanine, disrupts the cell cycle, causes alterations in transcription, eventually leading to cell death.
Clinical trials: Involved in over 30 trials in U.S. Studies in Europe have shown promise for treating soft tissue sarcoma, a rare form of cancer that has had no new treatments in 20 years. Also, shows promise in treating drug-resistant forms of cancer possibly by interfering with p-glycoprotein production.



Strategic bond disconnections for Ecteinascidin 743.

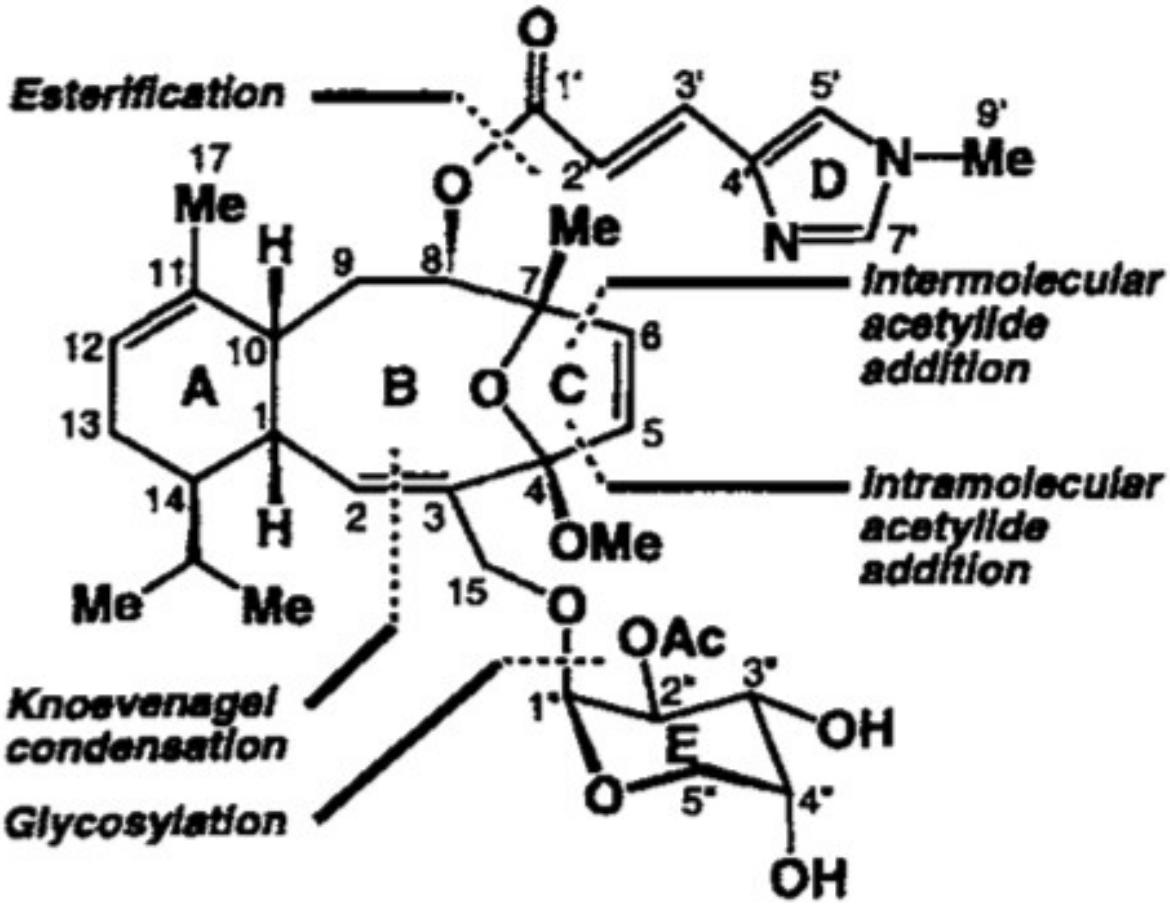

1. TBSCl
2. DIBAL-H
3. PDC
(97% overall)
piperidine, AcOH
toluene, 25° C, 18 h
(92%)
1. DPPA, NEt3
toluene, 70 ° C, 2 h
2. BnOH, 70 ° C, 1 h
(89%)
1. [Rh{(COD)-(R,R)-DIPAMP}]+BF4-, H2 (3 atm)
(100%, 96% ee)
2. H2, 10% Pd/C, EtOAc
(100%)
1. BF3•OEt2, DCM, 4 Å M.S., (73%)
2. H2, 10% Pd/C
100%
1. AllylOCOCl, pyr.
2. HCl/AcOH, 110° C
3. TBSCl
(>90% overall)
1. CIP, HOAt
NEt3, 0→25° C
1. AllylBr, Cs2CO3, DMF
2. LiAlH2(OEt)2, Et2O, -78°C
3. KF, MeOH
0.6 M CF3SO3H, H2O/CF3CH2OH (3:2), BHT, 45° C
(57% overall from THIQ)
LiAlH2(OEt)2
Et2O, 0°C
then, AcOH, aq. KCN
(87%)


1. Tf2NPh, NEt3
4-DMAP, DCM
2. TBSCl, then KF
3. MOMCl, i-Pr2NEt
(65% overall)
1. n-Bu3SnH,
PdCl2(PPh3)2
AcOH, DCM
2. formalin,
NaCNBH3
AcOH, ACN
(95% overall)
1. PdCl2(PPh3)2, LiCl,
AcOH, Me4Sn, NMP
(94%)
2. (PhSeO)2O,
DCM (82%)
1. TBAF
2. EDC, HOBt
(83% overall)
Tf2O, DMSO
-40° C
then, i-Pr2NEt;
t-BuOH, then
Barton's base,
then Ac2O
(79%)
Barton's base
1. n-Bu3SnH,
Pd(PPh3)2Cl2
AcOH, DCM
(84%)
2. DBU, DMF
DCM, (70%)
silica gel
(82%)
1. TFA, H2O/THF
2. AgNO3, ACN/H2O
(77% overall)
ecteinascidin 743

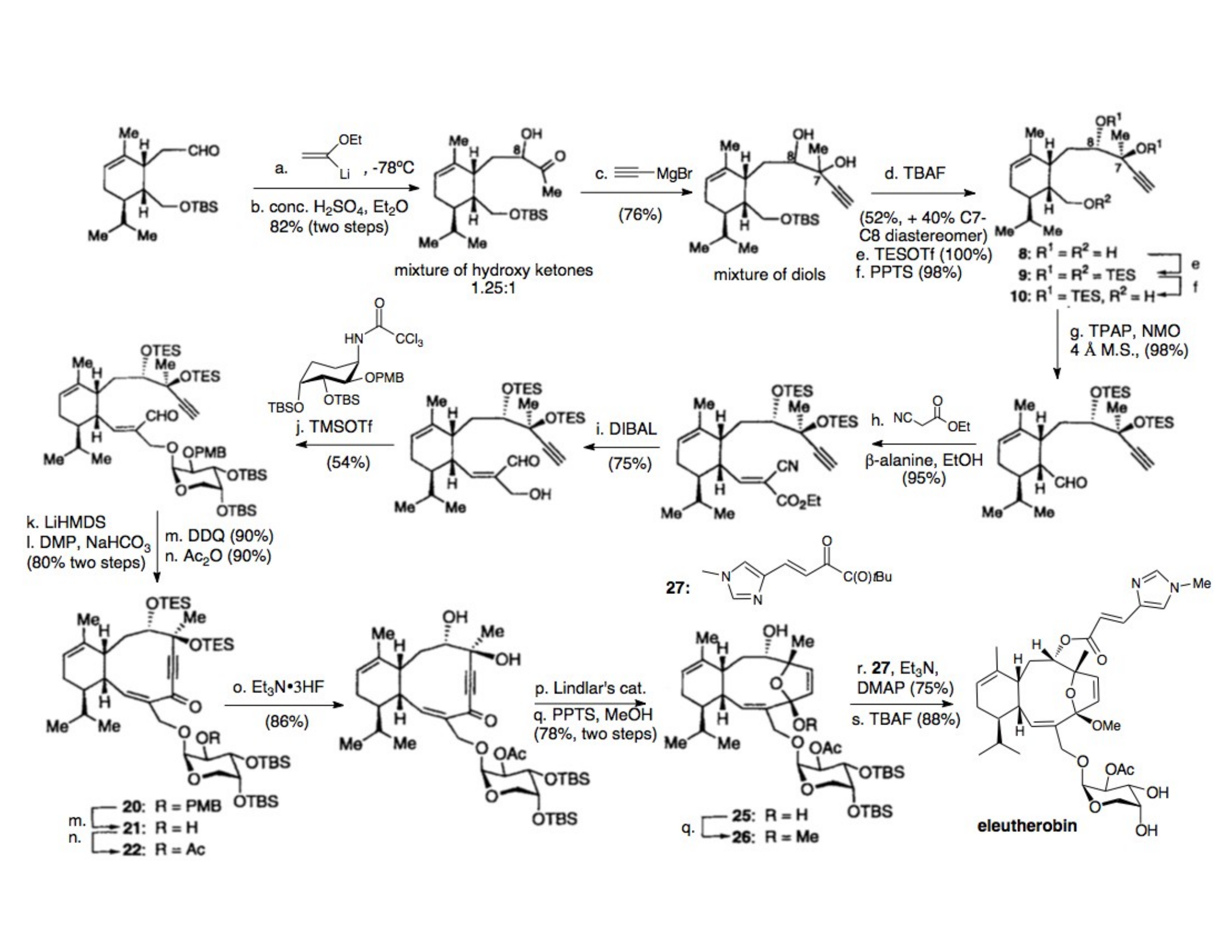


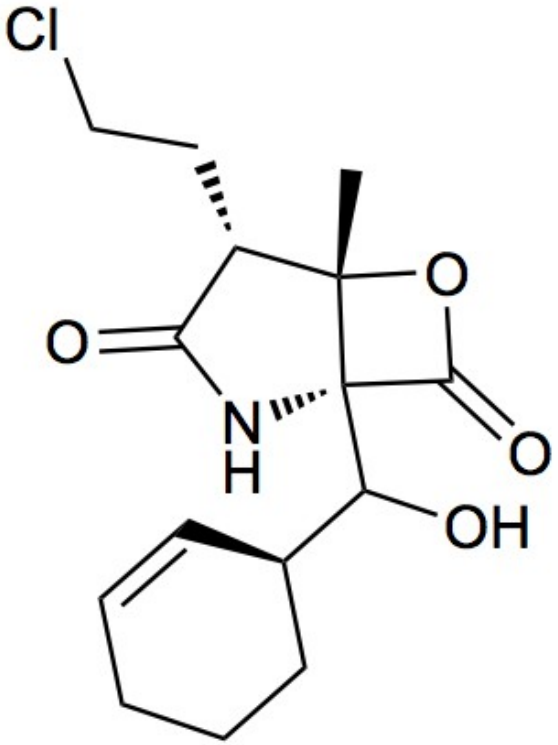
eleutherobin

Isolation: First isolated from *Eleutherobia sp.* collected in Australia in 1995 by William Fenical's lab at Scripps Institution of Oceanography. Also recently isolated from a Caribbean coral *Erythropodium caribaeorum*.
Total Synthesis: K.C. Nicolaou, Floris van Delft, Takashi Ohshima, et al. *ACIE*, **1997**, *36*, 2520-2524. Nicolaou group also published synthesis of Sarcodyctins (similar to eleutherobin) and analogs via solid phase synthesis.
Mechanism of action: Mechanism of action similar to Taxol. Binds to and polymerizes tubulin.
Clinical trials: Currently in preclinical status.



Strategic bond disconnections for eleutherobin.

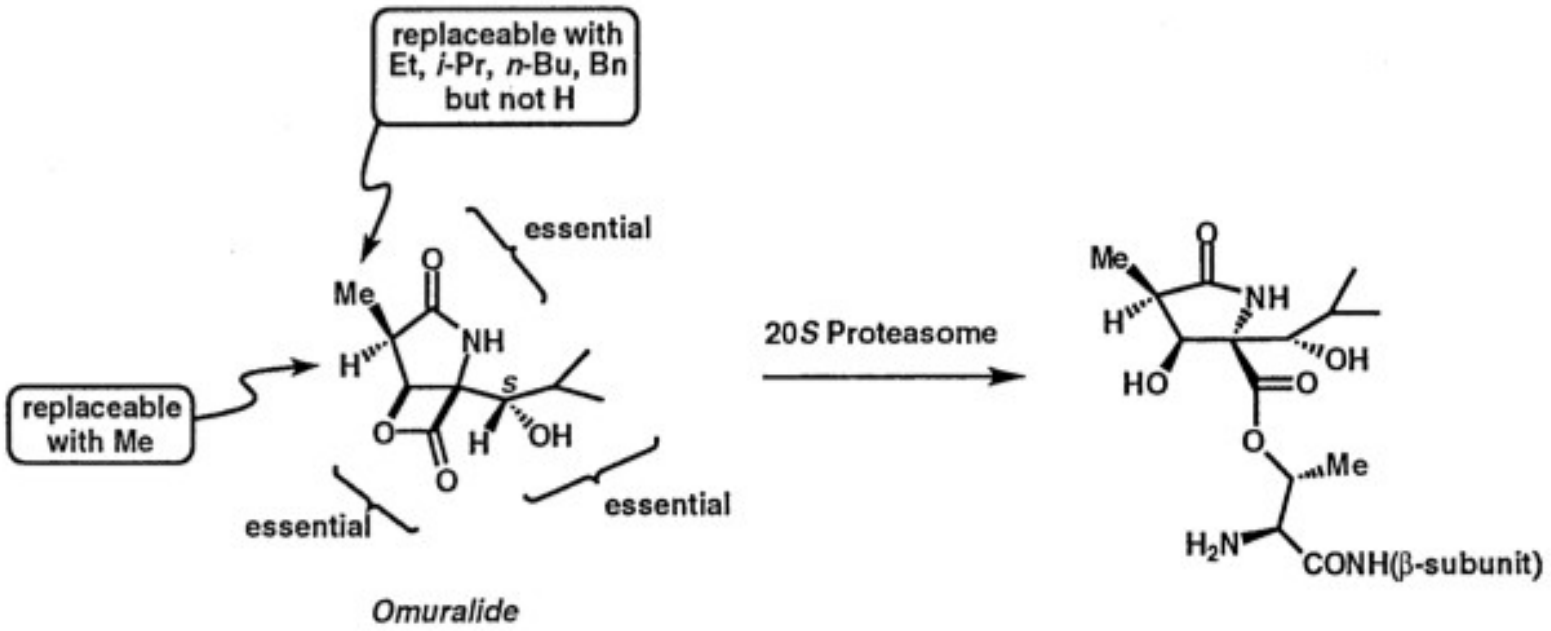

a. , -78°C
b. conc. H_2SO_4, Et_2O
82% (two steps)
mixture of hydroxy ketones
1.25:1
c. MgBr
(76%)
mixture of diols
d. TBAF
(52%, + 40% C7-C8 diastereomer)
e. TESOTf (100%)
f. PPTS (98%)
8: $R^1 = R^2 = H$
9: $R^1 = R^2 = TES$
10: $R^1 = TES$, $R^2 = H$
g. TPAP, NMO
4 Å M.S., (98%)
h.
β-alanine, EtOH
(95%)
i. DIBAL
(75%)
j. TMSOTf
(54%)
k. LiHMDS
l. DMP, $NaHCO_3$
(80% two steps)
m. DDQ (90%)
n. Ac_2O (90%)
o. Et_3N•3HF
(86%)
p. Lindlar's cat.
q. PPTS, MeOH
(78%, two steps)
r. 27, Et_3N, DMAP (75%)
s. TBAF (88%)
27:
20: R = PMB
21: R = H
22: R = Ac
25: R = H
26: R = Me
eleutherobin



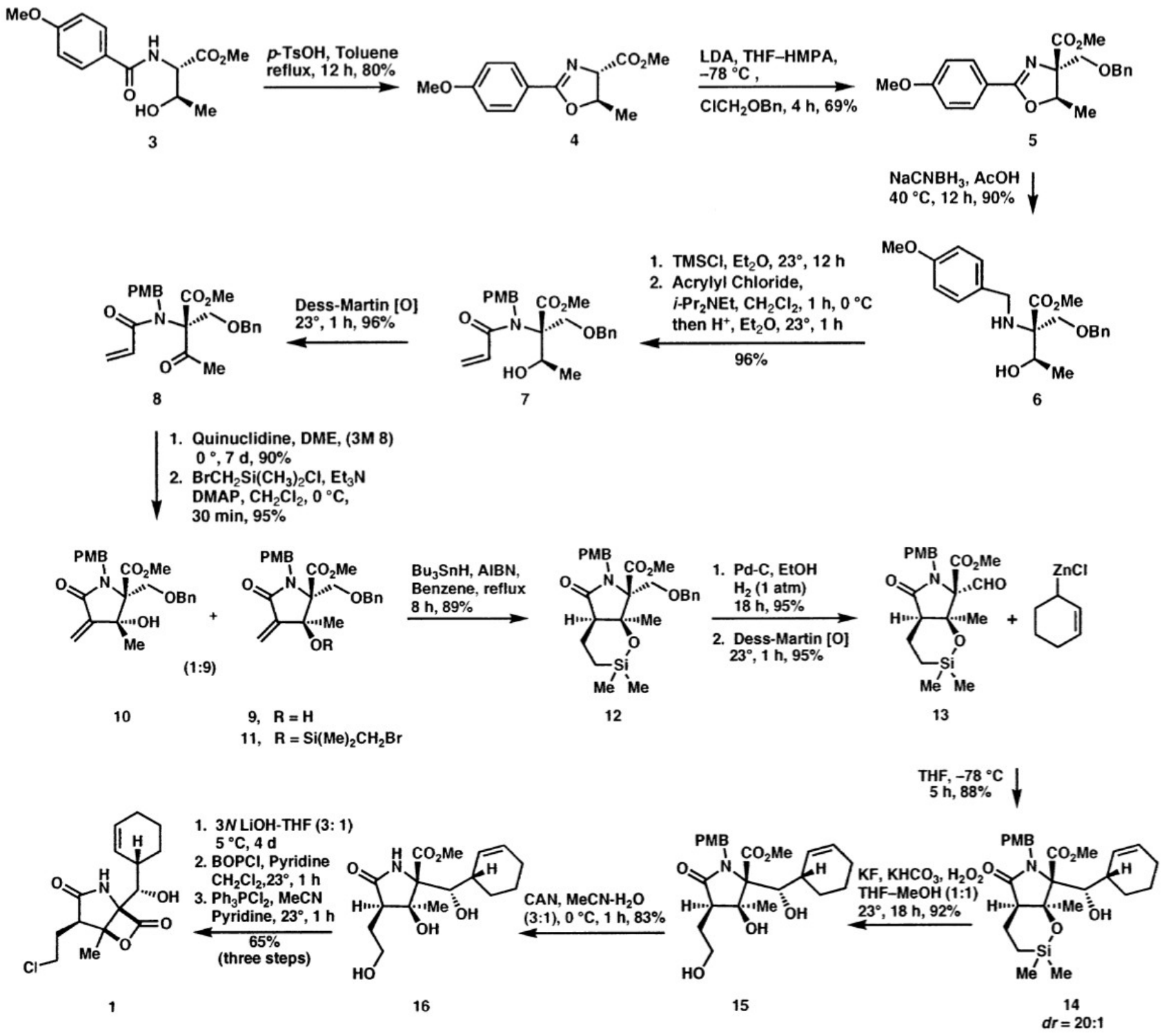
salinosporamide A

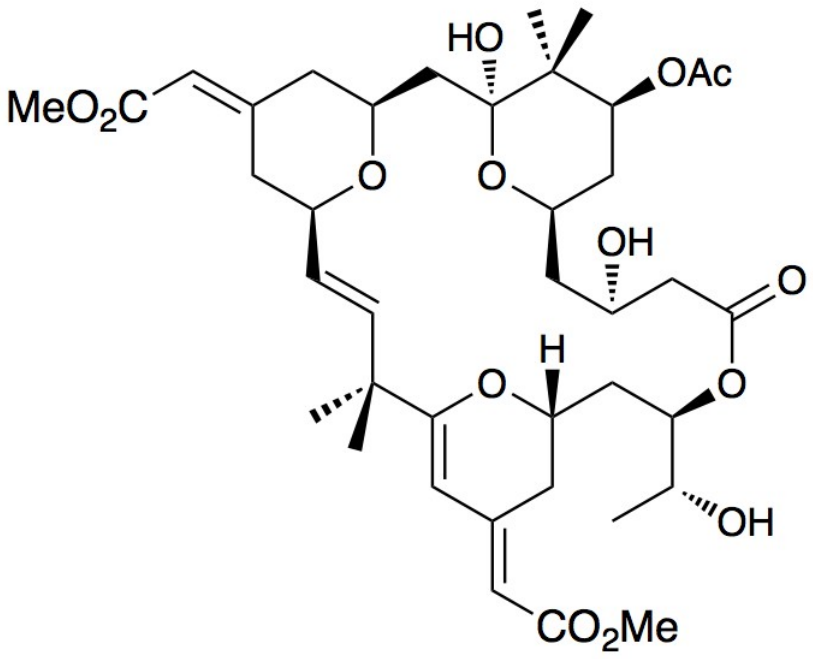
Isolation: Isolated from bacteria of the genus *Salinospora* by William Fenical (SIO) in 2003.
Total Synthesis: Leleti Rajender Reddy, P. Saravanan, and E. J. Corey. *JACS*, **2004**, *126*, 6230-6231.
Mechanism of action: Potent inhibitor of the proteasome by covalently binding to the active site threonine residues of the 20S proteasome.
Clinical trials: In vitro studies have shown salinosporamide A to have potent activity against several cancer cell lines. Proceeding through several phase I trials as a single agent against multiple myeloma, solid tumors, or lymphoma.

Summary of SAR done by Corey on lactacystin and analogs.



Li, W.; Corey, E.J. *Chem. Pharm. Bull.* **1999**, *47*, 1.

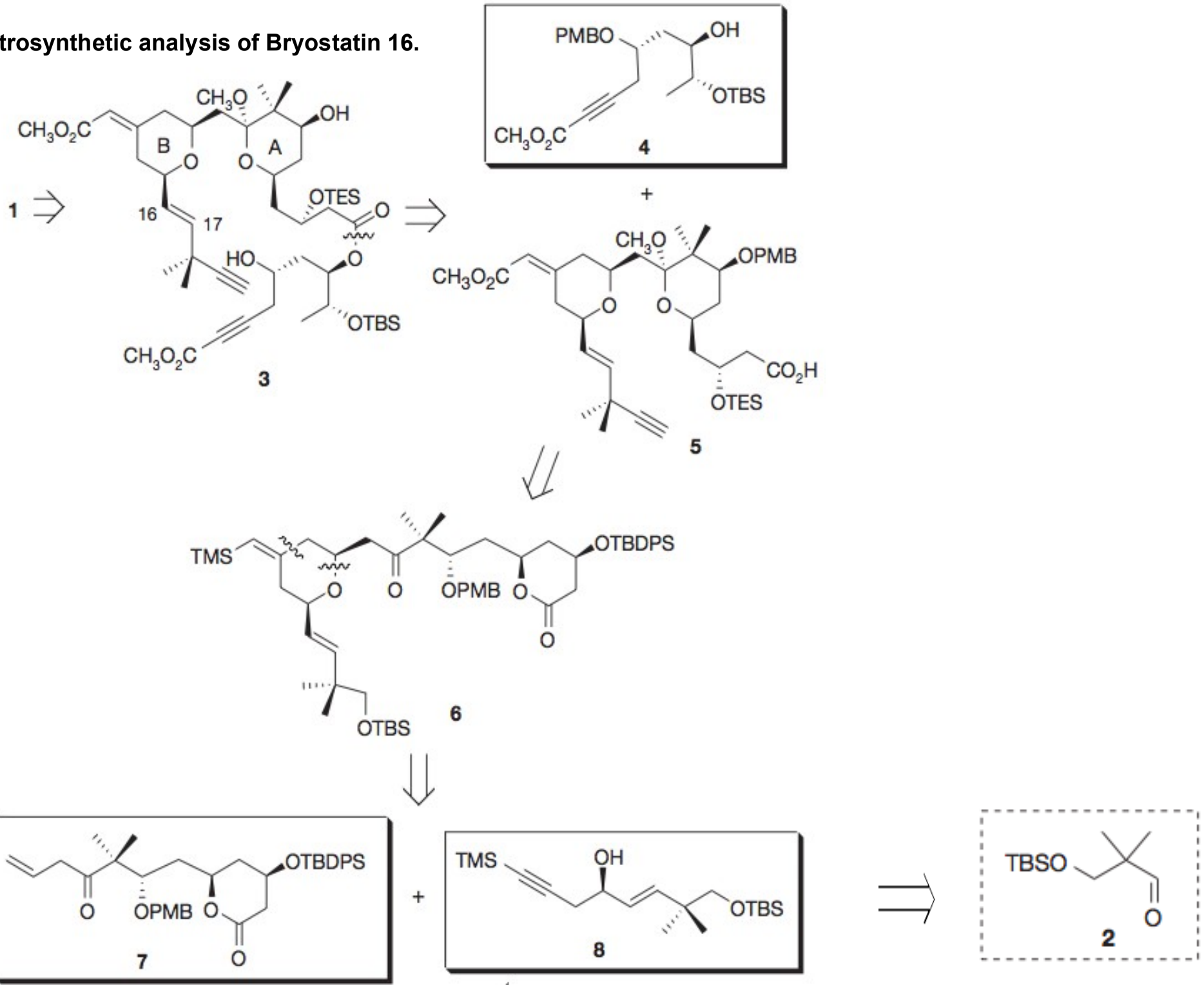

3
p-TsOH, Toluene
reflux, 12 h, 80%
4
LDA, THF–HMPA,
–78 °C ,
ClCH2OBn, 4 h, 69%
5
NaCNBH3, AcOH
40 °C, 12 h, 90%
6
1. TMSCl, Et2O, 23°, 12 h
2. Acrylyl Chloride,
i-Pr2NEt, CH2Cl2, 1 h, 0 °C
then H+, Et2O, 23°, 1 h
96%
7
Dess-Martin [O]
23°, 1 h, 96%
8
1. Quinuclidine, DME, (3M 8)
0 °, 7 d, 90%
2. BrCH2Si(CH3)2Cl, Et3N
DMAP, CH2Cl2, 0 °C,
30 min, 95%
(1:9)
10
9, R = H
11, R = Si(Me)2CH2Br
Bu3SnH, AIBN,
Benzene, reflux
8 h, 89%
12
1. Pd-C, EtOH
H2 (1 atm)
18 h, 95%
2. Dess-Martin [O]
23°, 1 h, 95%
13
THF, –78 °C
5 h, 88%
14
dr = 20:1
KF, KHCO3, H2O2
THF–MeOH (1:1)
23°, 18 h, 92%
15
CAN, MeCN-H2O
(3:1), 0 °C, 1 h, 83%
16
1. 3N LiOH-THF (3: 1)
5 °C, 4 d
2. BOPCl, Pyridine
CH2Cl2,23°, 1 h
3. Ph3PCl2, MeCN
Pyridine, 23°, 1 h
65%
(three steps)
1



bryostatin 16

Isolation: Found in extracts of the bryozoan *Bugula neritina* collected in the Gulf of California and Gulf of Mexico. Recent work has shown that it is likely produced by the symbiotic bacteria *Endobugula sertula*.
Total Synthesis: Bryostatin 16: Barry Trost, Guangbin Dong. *Nature*, **2008**, *456*, 485-488. Synthesis described as “atom-economical” by Trost. Before Trost's synthesis only 3 of 20 bryostatins had been chemically synthesized.
Mechanism of action: Can bind to protein kinase C, an enzyme involved in the upregulation and downregulation of certain proteins.
Clinical trials: Bryostatin 1 involved in over 30 trials related to cancer. Trials using bryostatin 1 and its analogs have been disappointing when used alone as an anticancer agent, but when used in combination the drug shows more promise. Granted orphan drug status by FDA when used in combination with Taxol for esophageal cancer in 2001. Also being tested in trials as an anti-Alzheimer's agent.

Retrosynthetic analysis of Bryostatin 16.



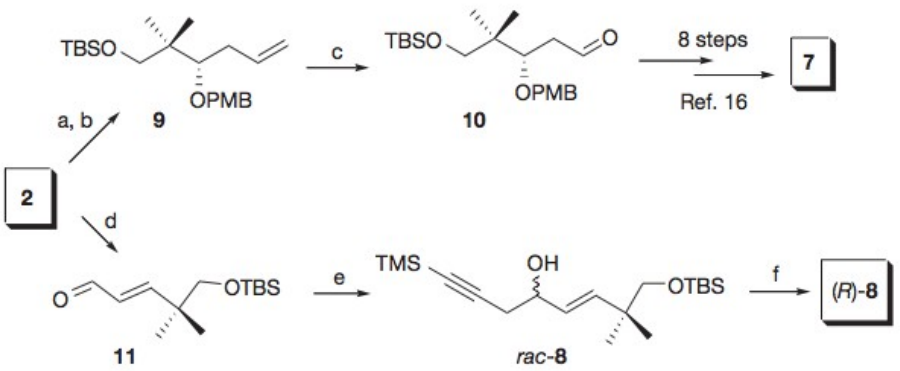


Figure 3 | Synthesis of alkene 7 and alkyne 8. Reaction conditions: (a) (–)-$(Ipc)_2B(allyl)$, Et_2O, –90 °C, 67%, 94% enantiomeric excess (e.e.); (b) PMB-Br, NaH, DMF, 90%; (c) OsO_4 (2 mol%), 2,6-lutidine, $NaIO_4$, dioxane/water (3:1), 87%; (d) (*Z*)-1-bromo-2-ethoxyethene, *t*-butyllithium, $(CH_3)_2Zn$, then **2**, $(C_2H_5)_2O$, –78 °C; then $NaHSO_4$, room temperature (20–25 °C), 97%; (e) (3-bromo-1-propynyl)-trimethylsilane, indium powder, InF_3 (10 mol%), THF, 65 °C, 68%; (f)(i) Dess–Martin periodinane, $NaHCO_3$, DCM; (f)(ii) (*S*)-2-methyl-CBS-oxazaborolidine (5 mol%), catecholborane, DCM, –78 °C, 90%, 90% e.e. over two steps. Ipc, isopinocamphenyl; DMF,

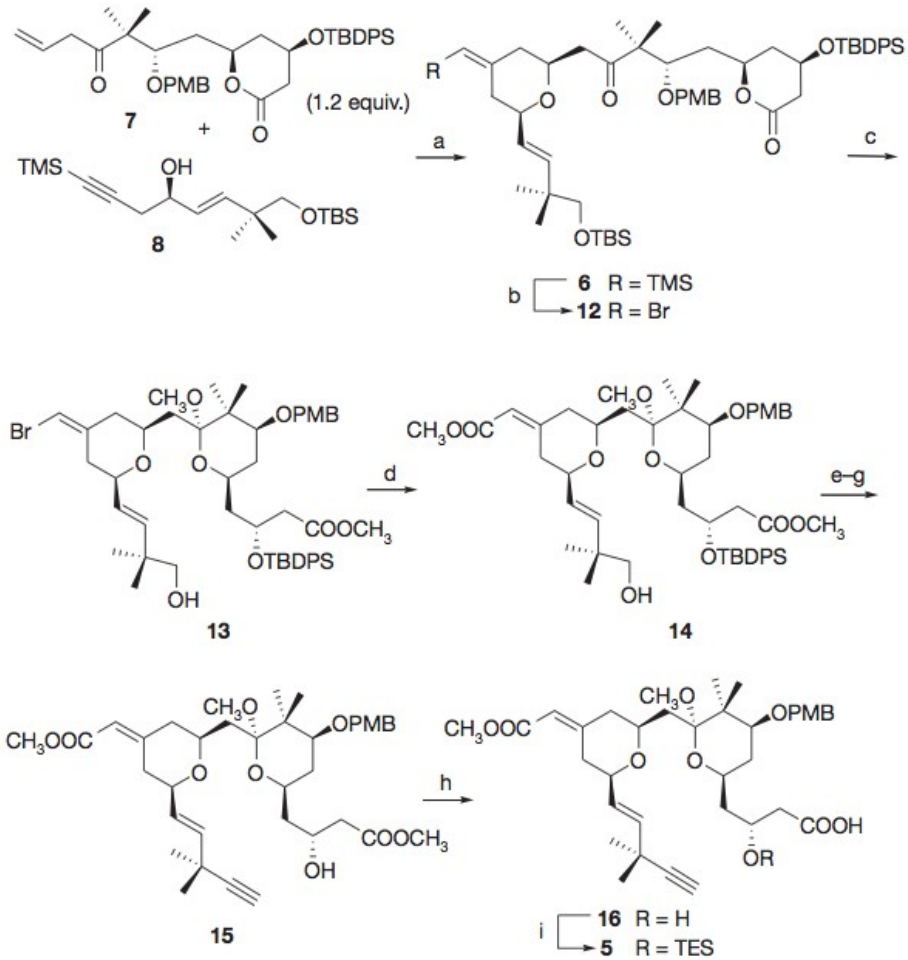
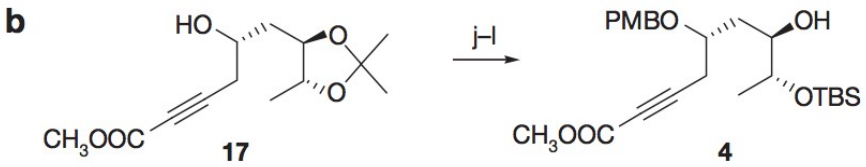


Figure 4 | Synthesis of acid 5 and alcohol 4. a, Synthesis of **5**. Reaction conditions: (a) $CpRu(CH_3CN)_3PF_6$ (13 mol%), DCM, 34% (80% b.r.s.m.); (b) NBS, DMF, 98%; (c) CSA (10 mol%), CH_3OH, 0 °C, 93–96%; (d) $PdCl_2(CH_3CN)_2$ (10 mol%), dppf (30 mol%), CO (1 atm), CH_3OH, $(C_2H_5)_3N$, DMF, 80 °C, 83% (90% b.r.s.m.); (e) Dess–Martin periodinane, $NaHCO_3$, DCM, 88%; (f) Ohira–Bestmann reagent, K_2CO_3, CH_3OH, 97%; (g) TBAF, HOAc, THF, 90% (96% b.r.s.m.); (h) $(CH_3)_3SnOH$, DCE, 80 °C, 84%; (i) TESOTf, 2,6-lutidine, DCM, −10 °C to 0 °C, 76–79%. **b**, Synthesis of **4**. Reaction conditions: (j) $Cu(OTf)_2$ (3 mol%), $PMBOC(NH)CCl_3$, toluene, –10 °C; (k) PPTS, CH_3OH, 93% over two steps; (l) TBSOTf, 2,6-lutidine, DCM, –78 °C, 71%. Cp, cyclopentadienyl; b.r.s.m., based on



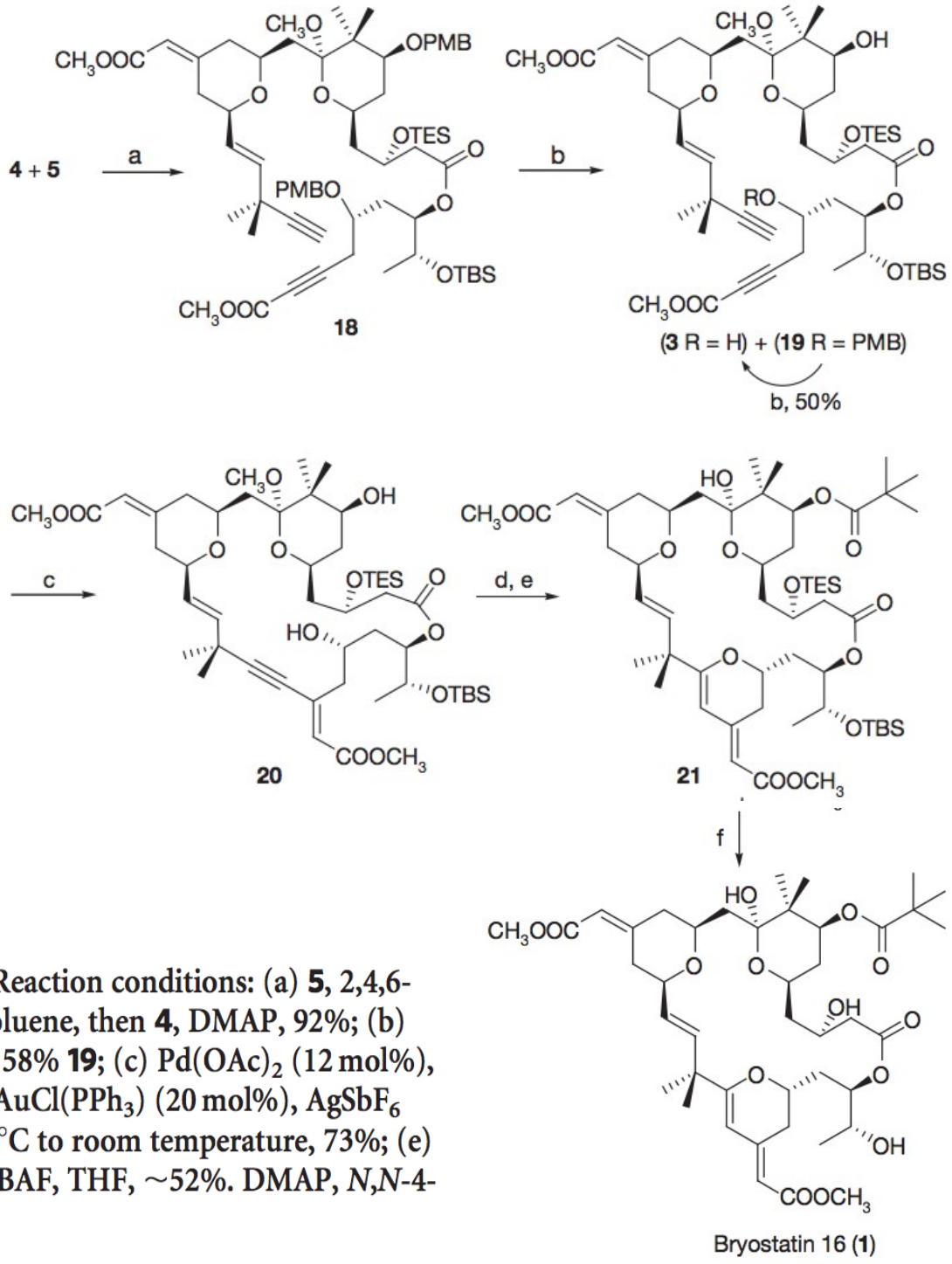


Figure 5 | Synthesis of bryostatin 16. Reaction conditions: (a) **5**, 2,4,6-trichlorobenzoyl chloride, $(C_2H_5)_3N$, toluene, then **4**, DMAP, 92%; (b) DDQ, pH 7.0 buffer, DCM, 46% **3** and 58% **19**; (c) $Pd(OAc)_2$ (12 mol%), TDMPP (15 mol%), toluene, 56%; (d) $AuCl(PPh_3)$ (20 mol%), $AgSbF_6$ (20 mol%), $NaHCO_3$, DCM/CH_3CN, 0 °C to room temperature, 73%; (e) Piv_2O, DMAP, DCM, 50 °C, 62%; (f) TBAF, THF, ~52%. DMAP, *N*,*N*-4-